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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,211	11/07/2003	Dean G. Hafeman	100/18101	2927

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EXAMINER	
YANG, NELSON C	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 12/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/705,211	HAFEMAN ET AL.	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *21-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of claims 1-20 in the reply filed on October 17, 2005 is acknowledged.

2. Claims 21-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 17, 2005.

3. Claims 1-41 are currently pending.

4. Claims 1-20 are under examination.

5. Claims 21-41 have been withdrawn.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 6-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. With respect to claim 6, it is unclear if applicants are claiming that the nucleic acid itself is comprised of two or more fluorescent labels and whether this includes the at least one fluorescent label associated with the nucleic acid recited in claim 5, or if the fluorescent labels are also associated with the nucleic acid.

9. With respect to claim 7, it is unclear if a biotinylated nickel chelator that binds nickel to the wall surface of the binding channel region is actually being claimed, or if applicant is merely

reciting that the streptavidin can bind a biotinylated nickel chelator that binds nickel to the wall surface of the binding channel region.

10. The remaining claims are indefinite due to their dependence on an indefinite claim.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claims 1, 2, 12-16, 18, 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuhr et al [US 6,294,392].

With respect to claim 1, Kuhr et al teach a method of using a flow through microfluidic (e.g. capillary) biosensor wherein binding partner "probes", specific to various analytes are immobilized in different sections of a capillary channel, e.g. using photolabile biotin/avidin technology (column 2, lines 10-18). The sample is then flushed through the capillary, so that the target analytes are bound to the binding partners (capture agents) immobilized on the capillary wall and the rest of the sample is eluted from the capillary and finally, the complexed (bound) analyte is released along the entire length of the channel and flushed past a detector (column 2, lines 19-30).

13. With respect to claim 2, 20, Kuhr et al teach that multiple analytes, of the same species of molecule (e.g., all nucleic acids), or of different species (e.g. proteins and nucleic acids), can be diagnosed by using a single biosensor in this manner (column 2, lines 30-36).

14. With respect to claim 12, Kuhr et al teach that binding partner "probes", specific to various analytes are immobilized in different sections of a capillary channel (column 2, lines 10-18).

15. With respect to claim 13, Kuhr et al teach that the channel can be formed from porous particles (column 9, lines 63-65).

16. With respect to claims 14-15, Kuhr et al teach that the fluid flow can be induced by a pressure difference and/or by electroosmotic flow (column 3, lines 20-30).

17. With respect to claim 16, release conditions can be induced by high temperature, denaturants, high or low pH (column 21, lines 1-10).

18. With respect to claim 18, the probes may be bound at a defined ionic strength and pH. (column 6, lines 5, lines 20-65).

19. Claims 1, 2, 11, 13-15, 17, 19, 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al [US 6,344,326].

20. With respect to claim 1, Nelson et al teach a method comprising the steps of: 1) the flow-through incubation of analytes of interest such as cells and antibodies specific to cell surface antigens; 2) the addition of surface-activated magnetic beads which bind with the antibodies followed by another flow-through incubation step; 3) application of a magnetic field for the affinity capture of the bead-antibody-analyte complex (column 23, lines 60-67) in enrichment channels (column 22, lines 41-43) and 4) the magnetic release of the complex (column 24, lines

1-3). The released cells then move through a main electrophoretic channel to a detection region (column 15, lines 5-15).

21. With respect to claims 2, 20, the analytes of interest can be proteins (column 27, lines 5-11). Therefore the antibodies would be protein-binding moieties.

22. With respect to claim 11, Nelson et al teach that a dye terminator can be employed in the reaction to provide a chromophore for fluorescence detection of the amplified DNA portions such that each resulting amplified DNA has a functional group at the 5' end of each strand, and carries the chromophore (column 33, lines 30-50).

23. With respect to claim 12, Nelson et al teach that the enrichment region of the channel may comprise binding members covalently bound to an insoluble matrix such as the wall of the channel (column 6, lines 5-25).

24. With respect to claim 13, Nelson et al teach surface-activated magnetic beads which bind with the antibodies followed by another flow-through incubation step and application of a magnetic field for the affinity capture of the bead-antibody-analyte complex (column 23, lines 60-67) in enrichment channels (column 22, lines 41-43).

25. With respect to claim 14, the flow through the enrichment zone can be controlled by application of a pressure gradient (column 34, lines 50-55).

26. With respect to claim 15, Nelson et al teach that the fraction of interest is driven electrokinetically (column 15, lines 50-55).

27. With respect to claims 17, 19, Nelson et al teach sandwich assays involving fluorescent means for detection (column 24, lines 5-11).

Claim Rejections - 35 USC § 103

28. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

29. Claims 3-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuhr et al [US 6,294,392] in view of Heikkila et al [Heikkila et al, Maternal serum second trimester AFP and hCG in preganancies with placenta previa, 2000, 20, 100-102].

Kuhr et al teach a method of using a flow through microfluidic (e.g. capillary) biosensor wherein binding partner "probes", specific to various analytes are immobilized in different sections of a capillary channel, e.g. using photolabile biotin/avidin technology (column 2, lines 10-18). The sample is then flushed through the capillary, so that the target analytes are bound to the binding partners (capture agents) immobilized on the capillary wall and the rest of the sample is eluted from the capillary and finally, the complexed (bound) analyte is released along the entire length of the channel and flushed past a detector (column 2, lines 19-30). Kuhr et al do not teach that the antibodies are specific for alpha-fetoprotein.

Heikkila et al, however, teach that prenatal screening for alpha-fetoprotein has been shown to be effective markers of Down syndrome in the second trimester of pregnancy (p.100, col.1).

Therefore, it would have been obvious to one of ordinary skill in the art for the antibodies in the method of Kuhr et al to be specific for alpha-fetoprotein, as suggested by Heikkila, in order to determine the likelihood of Down syndrome during prenatal screening in the second trimester of pregnancy.

30. Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al [US 6,344,326] in view of Heikkila et al [Heikkila et al, Maternal serum second trimester AFP and hCG in preganancies with placenta previa, 2000, 20, 100-102].

With respect to claims 3-4, Nelson et al teach a method comprising the steps of: 1) the flow-through incubation of analytes of interest such as cells and antibodies specific to cell surface antigens; 2) the addition of surface-activated magnetic beads which bind with the antibodies followed by another flow-through incubation step; 3) application of a magnetic field for the affinity capture of the bead-antibody-analyte complex (column 23, lines 60-67) in enrichment channels (column 22, lines 41-43) and 4) the magnetic release of the complex (column 24, lines 1-3). The released cells then move through a main electrophoretic channel to a detection region (column 15, lines 5-15). Nelson et al do not teach that the antibodies are specific for alpha-fetoprotein.

Heikkila et al, however, teach that prenatal screening for alpha-fetoprotein has been shown to be effective markers of Down syndrome in the second trimester of pregnancy (p.100, col.1).

Therefore, it would have been obvious to one of ordinary skill in the art for the antibodies in the method of Nelson et al to be specific for alpha-fetoprotein, as suggested by Heikkila, in order to determine the likelihood of Down syndrome during prenatal screening in the second trimester of pregnancy.

With respect to claim 5, Nelson et al teach DNA that carries a chromophore (column 33, lines 40-50) and a member of a affinity binding pair (column 33, lines 30-35), where the affinity binding pairs may include affinity purified monoclonal antibodies (column 6, lines 36-45).

31. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al [US 6,344,326] in view of Jensen et al [US 6,447,724].

With respect to claims 3-4, Nelson et al teach a method comprising the steps of: 1) the flow-through incubation of analytes of interest such as cells and antibodies specific to cell surface antigens; 2) the addition of surface-activated magnetic beads which bind with the antibodies followed by another flow-through incubation step; 3) application of a magnetic field for the affinity capture of the bead-antibody-analyte complex (column 23, lines 60-67) in enrichment channels (column 22, lines 41-43) and 4) the magnetic release of the complex (column 24, lines 1-3). The released cells then move through a main electrophoretic channel to a detection region (column 15, lines 5-15). Nelson et al do not teach that the nucleic acids comprise two or more fluorescent labels.

Jensen et al, however, teach nucleic acids incorporating one or more fluorescent labels (column 4, lines 30-40), which would allow for the detection and identification of a broad range of compounds (column 4, lines 9-21).

Therefore, it would have been obvious to one of ordinary skill in the art for the nucleic acids in the method of Nelson et al to comprise two or more fluorescent labels, as suggested by Jensen et al, in order to allow for the detection and identification of a broad range of compounds.

With respect to claims 7-10, Kuhr et al teach a method of using a flow through microfluidic (e.g. capillary) biosensor wherein binding partner "probes", specific to various analytes are immobilized in different sections of a capillary channel, e.g. using photolabile biotin/avidin technology (column 2, lines 10-18). The sample is then flushed through the

capillary, so that the target analytes are bound to the binding partners (capture agents) immobilized on the capillary wall and the rest of the sample is eluted from the capillary and finally, the complexed (bound) analyte is released along the entire length of the channel and flushed past a detector (column 2, lines 19-30). Kuhr et al do not teach that the wall surface has bound nickel chelators that bind nickel to the wall surface of the binding channel region of the microchannel.

Choudhary et al [US 6,107,038], however, teach that histidine tagged proteins can be reversibly immobilized on a surface in an oriented manner while their function is preserved, wherein the surface is silanized with 3-(mercaptopropyl)trimethoxy silane for 24 hour and treated with N^{α} N^{α} -bis-(carboxymethyl) maleimide for 1 hour and subsequently loaded with divalent metal cation e.g., Ni^{2+} (column 13, lines 15-40). Choudhary et al further teach that the binding of proteins to NTA is highly specific with reasonable affinities, and in addition fully reversible upon addition of competitive ligand such as imidazole (column 13, lines 25-38).

Therefore, it would have been obvious in the method of Kuhr et al that the wall surface has bound nickel chelators that bind nickel to the wall surface of the binding channel region of the microchannel, as suggested by Choudhary et al, in order achieve binding of proteins to NTA that is highly specific with reasonable affinities, and in addition which is fully reversible upon addition of competitive ligand such as imidazole.

Conclusion

32. No claims are allowed.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571) 272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571)272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

34. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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11/26/05